IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: Yong Soo CHONG
PORTER	Group Art Unit: 1617
Serial No.: 09/933,316	Confirmation No.: 7064
Filing Date: August 20, 2001	Customer No.: 20855
Title: EMBOLIC COMPOSITIONS WITH NON-CYANOACRYLATE RHEOLOGY MODIFYING AGENTS	

REPLY BRIEF UNDER 37 C.F.R. § 41.41

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

Appellants submit the following Reply Brief in Response to the Examiner's Answer mailed on February 8, 2007. This Reply Brief is submitted within two months of the date of mailing of the Examiner's Answer, *i.e.*, by April 8, 2007 and, accordingly, is timely filed. Appellants respectfully request that the decision of the Examiner be reversed.

STATUS OF THE CLAIMS

Claims 1, 3, 4, 9-11, 15-28 and 38-41 as shown in the Claims Appendix are appealed and remain variously rejected under 35 U.S.C. § 103(a).

STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed March 27, 2006, Appellants filed a Response with arguments and no amendments. An Advisory Action was mailed on July 13, 2006. No amendments were made in the Appeal Brief filed on November 20, 2006. Thus, all claims remained rejected for the reasons set forth in the Final Office Action, Advisory Action and Examiner's Answer mailed February 8, 2007.

GROUNDS OF REJECTION

A. Claims 1, 3-4, 9-11, 15-28 and 39-41 remain rejected under 35 U.S.C. §103(a) as allegedly obvious over WO 00/44287 (hereinafter "Krall") in view of U.S. Patent No. 6,203,779 (hereinafter "Ricci").

B. Claims 1, 3-4, 9-11, 15-28 and 38-41 remain rejected under 35 U.S.C. §103(a) as allegedly over Krall in view of Ricci and further in view of U.S. Patent No. 4,997,861 (hereinafter "Hechenberger").

RESPONSE TO EXAMINER'S ANSWER

A. Claims 1, 3-4, 9-11, 15-28 and 39-41 are not obvious over Krall in view of Ricci

To reiterate, the claims are drawn to the following combination of elements: (1) a matrix-forming component comprising alkyl cyanoacrylate monomers, a stabilizer and a plasticizer; (2) a solid aggregate comprising a radiopacifier; and (3) a polymeric non-cyanoacrylate rheology modifying agent having a molecular weight greater than 200,000 and selected from the recited group.

In support of the rejection over Krall and Ricci, it was again maintained that Krall's composition "only lacks a polymeric non-cyanoacrylate rheology modifying

agent that has an average molecular weight greater than 200,000." (Examiner's Answer, page 4). In addition, it was again asserted that Ricci discloses "the same polymers" as used in the instant claims because the language "about [molecular weight] 200,000" includes slightly greater than 200,000. (Examiner's Answer, pages 6-7). It was maintained that the motivation to combine the references flows from the compositions being used for the same purpose. (Examiner's Answer, pages 8-9, citing *In re Kerkhoven,* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Finally, it was asserted that the obviousness rejection is not based on hindsight reconstruction because it takes into account "only knowledge which was within the level of ordinary skill at the time the invention was made, and does not include knowledge gleaned only from the Appellant's disclosure." (Examiner's Answer, page 9).

1. Ricci does not teach or suggest "the same polymers" as used in the claimed compositions

As noted above, the Office continues to assert that Ricci teaches and/or suggests non-cyanoacrylate rheology modifying agents having molecular weights above 200,000, as claimed. (Examiner's Answer, pages 5-8).

In fact, Ricci does **not** teach rheology modifying agents as claimed. Contrary to the assertion in the Examiner's Answer, Ricci does **not** teach polymers having a molecular weight of "about" 200,000, let alone rheology modifying agents having molecular weights greater than 200,000, as claimed. The single reference in Ricci to molecular weights of 200,000 (cited in the Examiner's Answer) is not modified by the term "about." Rather, the term "about" is used to modify the lower molecular weight of the disclosed range – 50,000.[1] Ricci clearly states that 200,000 is the absolute upper limit of the molecular weight of the polymer (Ricci, col. 5, lines 23-35, emphasis added):

> Preferred biocompatible polymers include cellulose diacetate and ethylene vinyl alcohol copolymer. Cellulose diacetate polymers are either commercially available or can be prepared by art recognized procedures. In a preferred embodiment, the number average molecular weight, as

[1] Indeed, had Ricci intended to disclose polymers having molecular weights of "about 200,000," the cited passage would have read "from about 50,000 to about 200,000" as it does when referring to the range "from about 50,000 to about 75,000" earlier in the same passage.

> determined by gel permeation chromatography, of the cellulose diacetate composition is from about 25,000 to about 100,000 more preferably from about 50,000 to about 75,000 and still more preferably from about 58,000 to 64,000. The weight average molecular weight of the cellulose diacetate composition, as determined by gel permeation chromatography, is **preferably from about 50,000 to 200,000** and more preferably from about 100,000 to about 180,000. As is apparent to one skilled in the art, with all other factors being equal, cellulose diacetate polymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight polymers. Accordingly, adjustment of the viscosity of the composition can be readily achieved by mere adjustment of the molecular weight of the polymer composition.

Thus, Ricci does not teach or suggest that the molecular weight of the cellulose diacetate and ethylene vinyl alcohol copolymers should ever exceed 200,000 for any reason, including for the purpose of increasing viscosity. This reference is clear that 200,000 is the maximum average molecular weight of such cellulose diacetate polymers and that polymers of MW 200,000 (or less) provide more than sufficient viscosity. Indeed, Ricci teaches that preferred polymers have molecular weights significantly less than 200,000. Since Ricci's polymers function perfectly well when their molecular weights are 200,000 or well below, this reference actually teaches away from using rheology modifying agents as claimed.

In addition, there is nothing in Ricci regarding a solid cyanoacrylate containing matrix. Indeed, all Ricci's components all fluid until they are administered (Ricci, Abstract, emphasis added):

> Disclosed are methods for treating endoleaks arising from endovascular repair of abdominal aortic aneurysms. The disclosed methods involve the in situ sealing of endoleaks after placement of an endovascular prostheses in the abdominal aorta. Sealing of endoleaks is achieved by injection of either a biocompatible polymer or prepolymer **fluid** composition into the endoleak which composition in situ solidifies to seal the leak. Preferably, the biocompatible **fluid composition** comprises a contrast agent to allow the clinician to visualize the sealing process.

Moreover, all of Ricci's compositions are made up of one biocompatible polymer (cyanoacrylate or, alternatively, non-cyanoacrylate polymers having a molecular weight of 200,000 or less). Ricci draws a clear distinction between cyanoacrylate prepolymers

and non-cyanoacrylate polymers such as cellulose diacetate and unambiguously teaches that they are used separately (Ricci, Abstract and col. 1, lines 11-14, emphasis added):

> Sealing of endoleaks is achieved by injection of **either** a biocompatible polymer **or** prepolymer fluid composition into the endoleak which composition in situ solidifies to seal the leak.

As previously noted, Ricci's teachings that cyanoacrylates and non-cyanoacrylates such as cellulose diacetate are distinct compositions that are to be used in the alternative is also mirrored in the claims of this patent -- claim 1 is drawn to a fluid composition generally, claims 2-12 specify that the fluid composition is a biocompatible polymer; while claims 13-14 specify that the fluid composition include a biocompatible prepolymer.

Therefore, neither Ricci nor Krall teach or suggest compositions comprising non-cyanoacrylate rheology modifying agents having molecular weights greater than 200,000 and neither reference suggests combining cyanoacrylates and non-cyanoacrylates as claimed. Accordingly, it is irrelevant whether or not "both polymeric units of Krall and Ricci" are equally effective as embolic compositions" (Examiner's Answer, page 5), inasmuch as these references do not, in any combination, teach or suggest the particularly claimed compositions.

Furthermore, given the Office admits Krall and Ricci's compositions are equally effective individually, there is absolutely no reason the skilled artisan would have been motivated to combine them to arrive at the claimed subject matter.

Krall and Ricci do not teach or in any way suggest all the elements of the claimed compositions; do not provide any motivation to modify or combine their teachings as set forth in the rejection and, even if combined, would not give rise to compositions as claimed.

2. The rejection is improperly based on hindsight reconstruction

Thus, there is nothing in Krall or Ricci that would motivate the skilled artisan to (1) modify Ricci's polymers to have molecular weights greater than 200,000 and/or (2) combine such modified polymers with Krall's compositions. Moreover, the motivation

to combine Krall and Ricci is **not** based on knowledge available at the time of filing, but on knowledge gleaned from Appellant's particular disclosure.

An obviousness rejection is only proper when it is based on common knowledge available at the time of filing. As clearly set forth in the recent Federal Circuit case *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 80 USPQ2d 1641 (Fed. Cir. 2006) (and every other case regarding obviousness), the motivation to combine cannot be based on what would be obvious after the specification at issue is filed. This is improper hindsight reconstruction (*Dystar* at page 1656):

> As we recently explained in *Alza Corp. v. Mylan Labs.*, Inc., No. 06-1019, 2006 U.S. App. LEXIS 22616 [80 USPQ2d 1001] (Fed. Cir. Sept. 6, 2006), the suggestion test—as our motivation-to-combine inquiry has come to be known—"prevent[s] statutorily proscribed hindsight reasoning when determining the obviousness of an invention."

Moreover, the common knowledge relied upon must be clearly set forth (*Dystar* at 1649, emphasis added):

> Likewise, a close reading of *In re Lee* reveals that our objection was not to the Board's statement that "[t]he conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art without any specific hint or suggestion in a particular reference", but **its utter failure to explain the "common knowledge and common sense" on which it relied**.

In the case on appeal, the Examiner has improperly based the obviousness rejection on a finding of what would be obvious in light of Appellants' disclosure, rather than what would have been obvious at the time of filing and has failed to set forth the "common knowledge" allegedly relied upon.

As noted above, the rejection is maintained on the grounds that both rheology modifying agents with molecular weights greater than 200,000 and combining solid cyanoacrylates (Krall) with such rheology modifying agents was somehow "common knowledge" at the time of filing. (Examiner's Answer, pages 5-8). However, the Examiner has not provided sound reasons supporting why the claims would have been

obvious to the skilled artisan at the time of filing. The Office has not pointed to anything in the references or the common knowledge available at the time of filing that would motivate the skilled artisan to modify Ricci's polymers to have molecular weights over 200,000 and/or to combine Ricci and Krall. Indeed, at the time of filing, it was far from "common knowledge" that rheology modifying agents of molecular weights greater than 200,000 would be embolic, let alone they could be combined with solid cyanoacrylates as disclosed in Krall.

The Examiner has not shown that the common knowledge regarding embolic compositions at the time of filing includes any suggestion of compositions as claimed, comprising a solid cyanoacrylate and a rheology modifying agent having a molecular weight greater than 200,000 or that this common knowledge provides any reason to modify Ricci and combine it with Krall. As noted above in *Dystar*, a *prima facie* case of obviousness has not been made out because the Examiner's contention that the skilled artisan would have somehow had the knowledge to modify Ricci's non-cyanoacrylate polymers to have higher molecular weights than actually disclosed in this reference and then to combine these undisclosed rheology modifying agents with Krall's cyanoacrylates is completely unsupported by any reasoning "based on established scientific principles" that some advantage would have resulted from the hypothetical modifications.

It is only with Appellants' disclosure in hand that a skilled artisan would modify Ricci's rheology agents and combine Krall and with the modified Ricci compositions. *See In re Kotzab* 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) and *Amgen, Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious." *See,* also, *e.g.*, page 3, lines 18-20 and page 25, lines 15-25 of the specification:

> There is no suggestion or recognition [in Krall] that such properties can be improved by a non-cyanoacrylate rheology modifying agent. ...
>
> The composition has the desired viscosity and cohesive characteristics to administer into an ionic fluid environment, such as blood. The composition forms a solid structure upon contact with the ionic environment. ... The composition and method of present invention can be

> advantageously used to block blood flow to certain tissues, areas, or cavities in the vasculature.

Accordingly, because there is no evidence that a skilled artisan would have made the suggested combination at the time of filing, the rejection is an impermissible hindsight reconstruction.

The alleged motivation to combine (use as embolic compositions) is not present in the references or in the common knowledge available at the time of filing. Without the benefit of Appellants' disclosure, a skilled artisan would have had no motivation to, and no reasonable expectation that, modifying Ricci's rheology modifying agents to have molecular weights greater than 200,000 and then adding these agents to Krall's compositions would provide improved compositions, both in terms of embolic characteristics and delivery. Accordingly, a *prima facie* case of obviousness has not been (and indeed cannot be) presented by the Office, as such a rejection can only be based on improper hindsight reconstruction. Withdrawal of the rejection is in order.

3. Secondary considerations of non-obviousness: unexpected results

Furthermore, although not required because the Office has failed to present a *prima facie* case of obviousness, evidence regarding unexpected results is already of record and has not been considered by the Office.

As set forth in the Appeal Brief, the as-filed specification makes it clear that combining non-cyanoacrylate rheology modifying agents with known cyanoacrylate embolic resins significantly improves viscosity, cohesiveness, suspension of dense radiopacifiers, radiopacity, hydrolytic stability, adhesiveness to the target tissue and/or ease of delivery via microcatheter (decreases adhesiveness to the catheter). *See, e.g.,* as-filed specification, page 3, lines 22-30; page 7, lines 26-29; page 8, line 29 to page 9, line 5; and page 17, line 31 to page 18, line 7, which latter passage is reproduced below):

> A rheology modifying agent can impart properties of the liquid injectable composition, such as improved viscosity, improved cohesiveness, improved suspension, stability of dense radiopacifying powders and additional radiopacity. A solidified composition including a polymeric rheology modifying agent can have properties demonstrating improved

hydrolytic stability when compared to cyanoacrylate compositions containing pre-polymerized cyanoacrylate.

Thus, although a *prima facie* case of obviousness has not been made out (and indeed the references contain no supporting basis), additional factual evidence or record in the present case further supports to the non-obviousness of the claimed methods.

For all of the aforementioned reasons, the rejections under 35 U.S.C. § 103(a) based on Krall and Ricci should be withdrawn.

B. Claims 1, 3-4, 9-11, 15-28 and 38-41 are non-obvious over the cited references

For the reasons of record and as noted above, there is no combination of Krall and Ricci that render any of the claims on appeal obvious. Hechenberger does not cure the deficiencies of the combination of Krall and Ricci. Accordingly, claims 1, 3-4, 9-11, 15-28 and 38-41 are not obvious over Krall in view of Ricci and in further view of Hechenberger.

In sum, a *prima facie* case of obviousness has not been established. Krall and Ricci do **not** teach or suggest the rheology modifying agents of the claims and neither Krall, Ricci nor the common knowledge available at the time of filing teaches or suggests combining cyanoacrylates with non-cyanoacrylate rheology modifying agents as claimed. Therefore, without the benefit of Appellants' disclosure, a skilled artisan would not have been motivated to make a non-cyanoacrylate rheology modifying agent having a molecular weight greater than 200,000 and certainly would not have been motivated to combine this hypothetical rheology modifying agent with a matrix-forming component (alkyl cyanoacrylate monomers, a stabilizer and a plasticizer) and with a solid aggregate material. Accordingly, the rejections under 35 U.S.C. § 103 should be withdrawn.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are non-obvious over the cited references. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: March 13, 2007

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CLAIMS APPENDIX

1. A medical composition comprising

a matrix-forming component comprising alkyl cyanoacrylate monomers, a stabilizer and a plasticizer;

a solid aggregate material comprising a radiopacifier; and

a polymeric non-cyanoacrylate rheology modifying agent that has an average molecular weight greater than 200,000, wherein the cyanoacrylate rheology modifying agent is selected from the group consisting of poly(acrylates), poly(alkenes), poly(alkyl oxides), poly(amides), poly(carbonates), cellulosic polymers and copolymers, poly(dienes), poly(esters), poly(methacrylates), poly(saccharides), poly(siloxanes), poly(styrenes), poly(urethanes), poly(vinyl ethers), poly(vinyl esters), polymers and copolymers having high iodine content, and mixtures thereof.

3. The composition of claim 1, the solid aggregate material further comprising a second non-cyanoacrylate rheology modifying agent comprising an inorganic particulate material.

4. The composition of claim 1, wherein the non-cyanoacrylate rheology modifying agent is soluble in the alkyl cyanoacrylate monomers or in the plasticizer.

9. The composition of claim 1, wherein the non-cyanoacrylate rheology modifying agent and the plasticizer is the same material.

10. The composition of claim 1, wherein the non-cyanoacrylate rheology modifying agent comprises from greater than 0% to about 10%, by weight of the matrix-forming components.

11. The composition of claim 1, wherein the non-cyanoacrylate rheology modifying agent is a polymer comprises from about 1% to about 5%, by weight of the matrix-forming components.

15. The composition of claim 1, wherein the alkyl cyanoacrylate monomer is a compound of the formula $H_2C=C(CN)--C(O)OR$, wherein R is an alkyl group of about 1 to about 18 carbons.

16. The composition of claim 15, wherein the group represented by R is an alkyl group of about 4 to about 10 carbons.

17. The composition of claim 1, wherein the alkyl cyanoacrylate monomer is present in an amount of from about 20% to about 75%, by weight of the matrix-forming component.

18. The composition of claim 1, wherein the alkyl cyanoacrylate monomer is present in an amount of from about 30% to about 70%, by weight of the matrix-forming component.

19. The composition of claim 1, wherein the stabilizer is an inorganic acid, an organic acid, a free radical inhibitor, an antioxidant, or a mixture thereof.

20. The composition of claim 1, wherein the stabilizer is present in an amount of from about 50 ppm to about 500 ppm.

21. The composition of claim 1, wherein the radiopacifier is selected from the group consisting of Ta, TaO, Au, Pt, Zr, ZrO, bismuth subcarbonate, and barium sulfate.

22. The composition of claim 1, wherein the radiopacifier comprises radio-opaque particles with surface-modifying molecules adsorbed to or bonded to the surfaces of said particles for improving the stability of a suspension of said particles within said composition.

23. The composition of claim 1, wherein the radiopacifier is about 25% to about 100%, by volume of the solid-aggregate material.

24. The composition of claim 1, wherein the radiopacifier is about 60% to about 100%, by volume of the solid-aggregate material.

25. The composition of claim 1, wherein the plasticizer is selected from the group consisting of organic esters containing 10 or more carbon atoms and polymeric compounds having a glass transition temperature less than 20°C.

26. The composition of claim 1, wherein the plasticizer is selected from the group consisting of aromatic esters, alkyl esters, phthalate esters, citrate esters, glycerol esters, plant derived oils, animal derived oils, silicone oils, iodinated oils, vitamins A, C, E, and acetates and esters thereof, and mixtures thereof.

27. The composition of claim 1, wherein the plasticizer is about 10% to about 75%, by weight of the matrix-forming component.

28. The composition of claim 1, wherein the plasticizer is about 30% to about 60%, by weight of the matrix-forming component.

38. The composition of claim 3, wherein the inorganic particulate material is selected from the group consisting of fumed silica, silicatious earth, bentonite, and mixtures thereof.

39. The composition of claim 3, wherein the second non-cyanoacrylate rheology modifying agent is a particulate material comprising from greater than 0% to about 75%, by volume of the solid aggregate materials.

40. The composition of claim 3, wherein the second non-cyanoacrylate rheology modifying agent is a particulate material comprising from greater than 0% to about 40%, by volume of the solid aggregate materials.

41. The composition of claim 3, wherein the second non-cyanoacrylate rheology modifying agent is a particulate material comprises inorganic particles with surface-modifying molecules adsorbed to or bonded to the surfaces of said particles for improving the stability of a suspension of said particles within said composition.

EVIDENCE APPENDIX

No documents are submitted in the Evidence Appendix

RELATED PROCEEDINGS APPENDIX

Appellants are not aware of any related appeals or interferences which may be related to, directly affect, be directly affected by, or have any bearing on the Board's decision in the pending appeal. Accordingly, no documents are submitted with this Appendix.